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COMMISSION ON EPIDEMIOLOGICAL SURVEY
ARMED FORCES EPIDEMIOLOGICAL BOARD

SUMMARY OF THE ANNUAL REPORT
OF THE COMMISSION
FISCAL YEAR 1966

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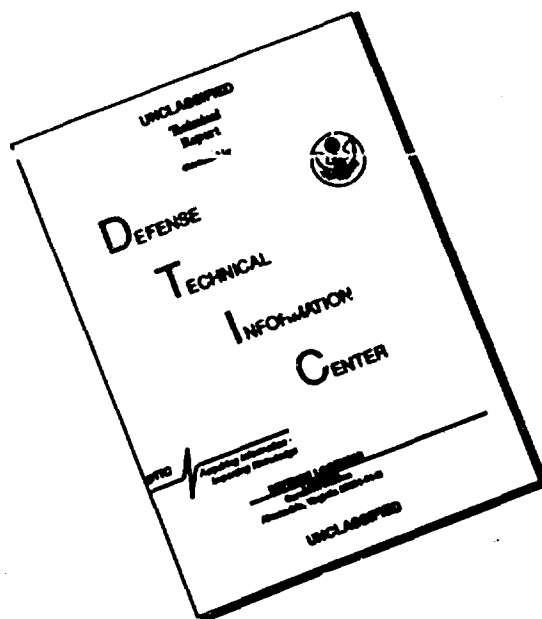
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MARCH 1967

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ARMED FORCES EPIDEMIOLOGICAL BOARD

SUMMARY OF THE ANNUAL REPORT
OF THE COMMISSION
FISCAL YEAR 1966

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MARCH 1967

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THE DIRECTOR'S SUMMARY REPORT

The Commission on Epidemiological Survey held its annual meeting at the Walter Reed Army Institute of Research on 9 September 1966. Senior representatives of the Department of Army, Navy and Air Force and the U. S. Army Medical Unit and other personnel at Fort Detrick who attended were:

U. S. Army Medical Unit

Colonel W. R. Beisel, MC
Captain M. K. Ward, USPHS
Lt Colonel K. R. Dirks, MC
Lt Colonel R. W. McKinney, MSC
Major M. I. Rapoport, MC
Major G. E. Shambaugh, III, MC
Captain A. C. Alevizatos, MC
Captain C. P. Craig, MC
Captain, R. D. Feigin, MC
Captain E. V. Staab, MC
Dr. G. Lust
Dr. V. G. McGann

U. S. Army

Colonel J. W. Cooch, MC, Walter Reed Army Institute of Research
Colonel L. P. Frick, MSC, Medical Research & Development Command
Colonel G. W. Johnston, MSC, Medical Research & Development Command
Colonel R. M. Nims, VC, Fort Detrick
Lt Colonel R. T. Cutting, MC, Medical Research & Development Command
Lt Colonel J. Einarson, MC, Office of The Surgeon General
Lt Colonel J. C. Fitzpatrick, MC, Medical Research & Development Command

U. S. Navy

Captain J. W. Millar, Bureau Medicine and Surgery
Commander L. W. Miller, Bureau Medicine and Surgery

U. S. Air Force

Colonel S. Lutz, Jr., MC, HQ, USAF, Office of The Surgeon General

Guests

Dr. Frank A. Carozza, Jr., Union Memorial Hospital, Baltimore, Maryland
Dr. Harold N. Glassman, Fort Detrick
Dr. Riley D. Housewright, Fort Detrick

Dr. Gustave Dammi, President of the Armed Forces Epidemiological Board, attended and made many helpful suggestions in connection with our mission. The Director expressed grateful appreciation to Captain Sidney A. Britten, USN, Executive Secretary of the Board, and to Miss Betty Gilbert, Administrative Assistant, for their continued assistance in conducting the Commission's activities.

The agenda of the one day's meeting was devoted to reviewing work completed or in progress by investigators of the U. S. Army Medical Unit and one of its contractors.

VENEZUELAN EQUINE ENCEPHALOMYELITIS VACCINE

Clinical studies of 40 persons given attenuated Venezuelan equine encephalomyelitis (VEE) vaccine revealed demonstrable viremia in 13 subjects and clinical symptomatology in 15 subjects. The clinical findings did not correlate with the presence of viremia. Transient electrocardiographic abnormalities were noted in 47.5% and transient leukopenia in 40% of the vaccinees. Eight individuals followed with daily electroencephalograms demonstrated no significant change subsequent to vaccination. There was no statistically significant correlation between any of these responses or combination of responses. The virologic studies demonstrated the presence of low grade viremia up to day 12 postinoculation. In view of the low level of viremia it appeared unlikely that vaccinees would infect Aedes aegypti mosquitoes. Members of the Commission on Viral Infections kindly studied the data and reached the same conclusion. Further studies are in progress.

METABOLIC CHANGES IN INFECTIOUS DISEASES

Intensive studies of metabolic and biochemical changes occurring in man during the incubation period and clinical course of various infectious diseases have been conducted. The objective of such appraisals has been to develop a better understanding of the fundamental nature of infectious processes and to search for objective clues which might lead to early diagnosis. In tularemic infection caused by aerosolization of virulent Pasteurella tularensis (SCHU-S strain) levels of certain blood amino acids are decreased from 12-36 hr before the onset of fever. The changes are greater in those persons with more severe illness. The loss does not result from excess urinary loss but perhaps from excess utilization by the liver and spleen. Amino acids are used for new protein synthesis.

There is a diurnal change in the concentration of blood amino acids in normal individuals. Following VEE vaccine administration at 0800 hr, there occurred an obliteration of the normal diurnal amino acid rhythm that began within 1 day and persisted for 4 days. When the same vaccine was administered to 20 other volunteers at 2000 hr, there was an early rise in blood amino acids of 2 days duration followed in turn by a fall to below normal concentrations for a total of 6 additional days. The changes in this latter group also included a loss of the diurnal rhythm,

but in addition several patients showed up to an 80-fold increase in proline, a marked increase in glutamic acid, and a depression in glutamine. Thus, the exposure at 2000 hr was accompanied by a distinct pattern of metabolic changes, some of which might involve an inhibition of the enzyme glutamine synthetase.

Changes in another enzyme, tryptophan pyrrolase were studied in the livers of mice infected with a small number of pneumococci. This infection was associated with a stimulation in the activity of this enzyme within 2 hr, but late in the infection the enzyme activity showed depression as it does during endotoxemia. The early induction of tryptophan pyrrolase was dependent upon the presence of an intact adrenal gland, an observation compatible with the known ability of cortisol to induce this enzyme. Late in infection, however, when plasma steroid levels were high, the enzyme activity fell and could not be stimulated by additional cortisol, an observation compatible with toxic inhibition of enzyme synthesis in a dying animal. Incidental to this study was the first description of a circadian change in this enzyme.

The infection-related stimulation of synthesis of new protein molecules within host cells is initiated by early sequential changes in deoxyribonucleic acid and ribonucleic acid (RNA) function within the cell. These were studied in several tissues of the intact mouse after infection with either Diplococcus pneumoniae or the Trinidad strain of VEE; similar studies with VEE were conducted in cultured tissue cells. It was possible to show differences in the direction of change in RNA and protein metabolism due to either the bacterial or viral infection. In addition, VEE infection of cultured cells was shown for the first time to be associated with induction of a new viral RNA synthetase; present techniques have not permitted identification of this enzyme in the intact animal host.

Studies of staphylococcal enterotoxin reveal that it is highly antigenic although the rate of antibody formation is slow. There appears to be a relationship between the level of circulating antibody and degree of resistance to enterotoxin in primates. Staphylococcal enterotoxin differs from bacterial endotoxins since pyrogenic tolerance as measured by reticulo-endothelial system reactivity is transient. When animals are pyrogenically refractory they react much less to intradermal injection of enterotoxin. These studies have broad implications and suggest that antibody inhibits skin reactivity.

The Commission, through the University of Maryland contract, has extended the studies relating to the protective efficacy of typhoid vaccine and pathogenesis of the disease. Typhoid vaccine K (acetone preserved) and L (phenol inactivated) protected volunteers against a low infectious challenge of 100,000 bacilli (expected to produce illness in 25% - ID₂₅). Aerosol exposure to an ID₂₅ of Salmonella typhosa failed to induce illness. This suggests that the respiratory tract is not a site of invasion. Penetration through pharyngeal or tonsillar tissue appears to be an unlikely mode of entry. Typhoid bacilli survive for 45 min or more in the stomach.

Organisms apparently multiply in the intestinal lumen and penetrate the mucosa. The lamina propria of the small intestine shows mild inflammatory changes during the incubation period after large oral inocula. Minimal changes occur after an ID₂₅ dose. Bacterial interference as a human host defense mechanism has been shown by studies with antibiotics given before infectious challenge. Nonabsorbable antibiotics reduce the numbers of intestinal bacteria altering the pH. Under these circumstances smaller numbers of bacilli cause clinical illness. Further interference studies are in progress.

The extensive studies of the effect of bacterial endotoxin in animals and human subjects show that during active infection with *S. typhosa* man acquires increasing hypersensitivity to the endotoxic component of the microbe. Intradermal testing with purified *S. typhosa* during illness reveals intensified 24-hr inflammatory lesions when compared to control preinfection responses and intravenous injection of the endotoxin elicits markedly hyperreactive pyrogenic responses and subjective toxic responses. The endotoxin tolerance mechanisms possessed by normal man remain intact. The repeated administration of endotoxin intermittently or by continuous intravenous infusion causes tolerance to develop rapidly within the framework of the hyperreactive state. In spite of marked activation of these tolerance mechanisms, the febrile and toxic course of the disease remains unchanged indicating that endotoxemia does not account for the sustained illness. Although endotoxemia may not account for sustained illness, the release of a relatively small bolus of endotoxin into the circulation during typhoid fever (or upon institution of appropriate antibiotic therapy), could readily induce an abrupt intensification of the febrile and toxic state in the hypersensitive host.

The vaccine trials indicate that the conventional typhoid vaccines are effective in protecting man against low infecting doses which might be expected in a water-borne exposure but would provide no protection from an exposure resulting from the consumption of heavily contaminated food containing more than 10,000,000 viable typhoid bacilli. Apparently the Vi antigen *per se* is not responsible for stimulating the protective antibody. Mechanisms involved in vaccine-induced resistance are not understood.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Resources, National Academy of Sciences-National Research Council.

In these studies the strictest standards which apply to human subjects as volunteers were adhered to.

The Executive Meeting was devoted to hearing of the progress in the staphylococcal enterotoxin B program and the need for evaluating several vaccines; VEE, EV plague, and Rocky Mountain spotted fever. The spotted fever vaccine studies will be conducted in collaboration with the Commission on Rickettsial Diseases.

Colonel Dan Crozier presented a paper describing the program of this Commission to the Association of Military Surgeons on 9 November 1966. The 1967 meeting of the Commission, scheduled for 7 and 8 September, will focus on a discussion of metabolic changes in infectious diseases.

Theodore E. Woodward, M.D.
Director
Commission on Epidemiological Survey

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13. ABSTRACT			
Forty volunteers were immunized with live attenuated Venezuelan equine encephalomyelitis virus vaccine and evaluated closely from clinical, laboratory, virologic and serologic standpoints. Some degree of reaction was noted in 37.5% of these individuals with 10% of them having 3+ reaction. Viremia was demonstrable in 32.5%; 47.5% had transient electrocardiogram abnormalities; 40% had transient leukopenia. There was no consistent positive or negative correlation between any of these responses or combination of responses.			
14. KEYWORDS			
Venezuelan equine encephalomyelitis Vaccine, attenuated Immunization			

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11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board
13. ABSTRACT An attenuated Venezuelan equine encephalomyelitis vaccine was studied in 40 men to determine viremia levels in order to determine the potential for mosquito transmission. It was concluded that the results of this study and prior artificial and direct feeding investigations indicated little or no such potential. It was proposed that the restriction against use of this vaccine strain be lifted.		
14. KEYWORDS Venezuelan equine encephalomyelitis Vaccine, attenuated Immunization Mosquito transmission		

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5. AUTHOR(S) (First name, middle initial, last name) FEIGIN, RALPH D.			
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13. ABSTRACT Blood amino acids appear to follow a circadian periodicity in a number of species. Respiratory acquired tularemia in man caused significant decreases in these acids prior to the onset of signs or symptoms. Live attenuated Venezuelan equine encephalomyelitis virus vaccine caused a reversal of normal diurnal rhythm of the acids regardless of time of inoculation, 0800 or 2000 hr. Staphylococcal enterotoxin B given to mice caused a rise in tryptophan, attributable to inhibition of tryptophan pyrrolase. The changes can be detected by a practical method using small amounts of blood.			
14. KEYWORDS Venezuelan equine encephalomyelitis Tularemia Staphylococcal enterotoxin B Vaccine Metabolism Amino acids Circadian rhythmicity			

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13. ABSTRACT Data on the serology of staphylococcal enterotoxin B (SEB) indicate that hemagglutination and toxin-combining activity were more sensitive than precipitation as indices of antibody, and that there was a relationship between circulating antibody and resistance to overt effects of SEB. Studies on antibody response suggest that SEB may be highly antigenic but that antibody development may be slow. Some factors that enter into the time of appearance and magnitude of response are challenge dose, previous experience or prechallenge antibody, and antitoxin treatment. These results were derived from studies in which monkeys received a single dose or several widely spaced doses of unaltered toxin. At the present time it would be unwise to predict the effect of multiple, closely spaced exposures to unaltered toxin or to toxoid preparations, or the response of another susceptible species, such as man.		
14. KEYWORDS Staphylococcal enterotoxin B Serology Immunology		

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4. DESCRIPTIVE NOTES (Type of report and inclusive dates)			
5. AUTHOR(S) (First name, middle initial, last name) CAROZZA, JR., FRANK A.			
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11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT Rabbits became pyrogenically refractory to staphylococcal enterotoxin B (SEB) after 4 daily intravenous injections. This state was transitory and disappeared completely within 9 days if animals are not repeatedly rechallenged. The state appears specific for SEB since refractory animals react normally to endotoxin and endogenous pyrogen. The refractory state is not mediated by a demonstrable circulating humoral protective factor nor generalized hyperactivity of the reticuloendothelial system. The occurrence of the state can be correlated with a significant diminution in skin sensitivity to enterotoxin. These data are compatible with the thesis that the fever produced in rabbits by SEB is mediated by a hypersensitivity reaction possibly of the delayed type.			
14. KEYWORDS Staphylococcal enterotoxin B Pyrogens Dose response Endotoxins			

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13. ABSTRACT		
Culture filtrates of anthrax toxin have been concentrated by ultracentrifugation, producing ultrafiltrate residue (UFR). Electrophoresis on paper, cellulose and gel discs has been carried out on UFR. Immunodiffusion and chromatography studies have also been conducted. Some fractions have not yet been identified, although some are related to previously known fractions, protective antigen, edema factor and lethal factor.		
14. KEYWORDS		
Anthrax Toxin Electrophoresis Chromatography Ultracentrifugation		

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13. ABSTRACT Both stimulatory and inhibitory influences have been observed to be at work on the tryptophan pyrrolase induction system. Adrenal steroids play a major role in the stimulatory aspects which we have noted. Data are not available as yet to state categorically whether changes in tryptophan pyrrolase activity in pneumococcus infection actually represent changes in enzyme synthesis or indirect changes in cofactor or substrate concentrations. It is apparent that additional studies will be required to define better the nature of the factors that mediate early host adaptive changes in infection.		
14. KEYWORDS Tryptophan Pneumococcal infection Enzymes Metabolism		

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13. ABSTRACT Electrophoresis on agarose gels separates ribonucleic acid (RNA) species discretely with good resolution. The method provides a rapid, sensitive way of screening RNA preparations for complexity of individual samples or in comparison of them from different sources or experimental conditions. The 6S RNA and the other minor components are apparently associated with ribosomes. The observation that the 6S RNA is associated with the ribosomes may be of value in elucidating its function. It may well be that this band is where messenger RNA is found. Although this method must still be refined in several ways, it is already very useful. An emphasis on alterations of specific RNA molecules as well as other metabolites, should provide significant contributions in order to define the host metabolic response to infections more precisely.		
14. KEYWORDS Metabolism Ribonucleic acid Deoxyribonucleic acid Ribonucleic acid, viral Electrophoresis		

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3. REPORT TITLE MECHANISMS OF ENDOTOXIN TOLERANCE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) GREISMAN, SHELDON E., YOUNG, EDWARD J., WOODWARD, WILLIAM E.		
6. REPORT DATE September 1966	7a. TOTAL NO. OF PAGES 3	7b. NO. OF REFS 2
8a. CONTRACT OR GRANT NO. DA-49-193-MD-2867		8b. ORIGINATOR'S REPORT NUMBER(S)
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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES A version has been published in Journal of Experimental Medicine 124:983, 1966.		12. SPONSORING MILITARY ACTIVITY U. S. Army Medical Unit Fort Detrick, Frederick, Maryland 21701
13. ABSTRACT The present observations, considered together with those of other investigators, support the hypothesis that pyrogenic unresponsiveness to endotoxin involves two distinct immunologic mechanisms. In terms of this hypothesis, the rapid reduction in febrile responsiveness to endotoxin is mediated by desensitization at the cellular level. With small doses of endotoxin, such as those employed in the present studies, this desensitization is primarily specific; with larger doses, nonspecific mechanisms are superimposed. So long as the subsequent doses of endotoxin are closely spaced or continuously infused, optimal conditions are provided for cellular desensitization and pyrogenic unresponsiveness to a given quantity of endotoxin can be induced rapidly and maintained without the requirement for antibody. However, as the interval between endotoxin challenge is lengthened, cellular desensitization wanes and tolerance becomes increasingly dependent upon those antibodies directed against the common toxophore groups responsible for endotoxin pyrogenicity which assist the reticuloendothelial system in the clearance and destruction of this molecule.		
14. KEYWORDS Endotoxin Pyrogens Staphylococcal enterotoxin B <u>Escherichia coli</u> endotoxin		

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3. REPORT TITLE TYPHOID FEVER: PATHOGENESIS AND PREVENTION			
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)			
5. AUTHOR(S) (First name, middle initial, last name) HORNICK, RICHARD B.			
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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315			
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY U. S. Army Medical Unit Fort Detrick, Frederick, Maryland 21701	
13. ABSTRACT Although the volunteer studies have shown typhoid vaccines to be effective against low dose challenge, the exact mechanism or mechanisms of this action are not apparent. Vi antigen did not appear to be necessary for the virulence of typhoid bacilli in man as in mice and probably was not important for the immunization of man. Hybrid strains of <u>Salmonella typhosa</u> have been isolated from the stools of volunteers.			
14. KEYWORDS Typhoid fever Pathogenesis Vaccines Immunity			

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3. REPORT TITLE STUDIES ON ROCKY MOUNTAIN SPOTTED FEVER: SEROLOGIC RESPONSE IN MAN TO VACCINATION WITH COMBINED EPIDEMIC TYPHUS, ROCKY MOUNTAIN SPOTTED FEVER AND Q FEVER VACCINE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) WISSEMAN, JR., CHARLES L., WOODWARD, THEODORE E.		
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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY U. S. Army Medical Unit Fort Detrick, Frederick, Maryland 21701
13. ABSTRACT A total of 17 men have now been given a combined epidemic typhus, Rocky Mountain spotted fever and Q fever vaccine without untoward local or systemic effects. Preliminary serologic testing has revealed little if any difference in response to the components of this vaccine as compared with response to monovalent vaccine after a single inoculation. Additional studies are in progress to extend these observations and to measure the immunogenic effect of multiple dose vaccination.		
14. KEYWORDS Rocky Mountain spotted fever Epidemic typhus Q fever Vaccines Serology		

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3. REPORT TITLE INFLUENCE OF TULAREMIA ON HUMAN INSULIN SECRETION		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) SHAMBAUGH, III, GEORGE E.		
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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES A version has been cleared for publication in Diabetes.		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board
13. ABSTRACT Serum insulin concentrations were measured serially in 7 nondiabetic subjects following a rapid intravenous (IV) glucose load during a preinfection control period, early clinical respiratory tularemia, and again in convalescence following therapy. Within 24 hr of onset of clinical illness the rate of glucose disappearance from the blood had diminished significantly. In contrast, there was a brisk onset of insulin response which reached higher peak concentrations and fell more slowly than the response observed during preinfection control period. The pattern during clinical illness was different from that described after IV glucose loading in maturity onset diabetes or obesity, and may have been influenced by glucocorticoid excess. The magnitude of insulin response during clinical illness was significantly increased and was directly related to height of fever. In contrast, the rate of glucose disappearance was inversely related to fever. The inverse relationship of the magnitude of insulin output to the rate of glucose disappearance suggested a peripheral inhibition of insulin action during infection. Although fever may have played a role during acute illness, the persistence of an abnormal insulin response in 1 patient during convalescence suggested that this change was not dependent upon fever alone.		
14. KEYWORDS Tularemia Metabolism Diabetes Insulin		

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3. REPORT TITLE COMMISSION ON EPIDEMIOLOGICAL SURVEY, ARMED FORCES EPIDEMIOLOGICAL BOARD, SUMMARY OF THE ANNUAL REPORT OF THE COMMISSION, FISCAL YEAR 1966		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) Summary of the Annual Report, Fiscal Year 1966		
5. AUTHOR(S) (First name, middle initial, last name) A. C. ALEVIZATOS, R. W. MCKINNEY, R. D. FEIGIN, V. G. MCGANN, F. A. CAROZZA, JR., M. K. WARD, M. H. WILKIE, A. BUZZELL, G. LUST, M. I. RAPOPORT, S. E. GREISMAN, E. J. YOUNG, W. E. WOODWARD, C. L. WISSEMAN, JR., R. B. HORNICK, T. E. WOODWARD, G. E. SHAMBAUGH, III		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY U. S. Army Medical Research and Development Command, Office of The Surgeon General, Department of the Army, Washington, D. C.	
13. ABSTRACT Progress is reported in selected areas of research in medical defense aspects of biological agents by the U. S. Army Medical Unit and one contractor.		
14. KEYWORDS Venezuelan equine encephalomyelitis Rocky Mountain spotted fever Q fever Epidemic typhus Tularemia Typhoid fever Anthrax toxin Mosquitoes Metabolism Staphylococcal enterotoxin B Endotoxin Vaccines		

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